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TITLE: Elucidation of Molecular Alterations in Precursor Lesions of Ovarian Serous Carcinoma

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Introduction

We have used this Development award to successfully compete for the Consortium award in 2011 (DOD Award W81XWH-11-2-0230: “*Prevention of Ovarian High-Grade Serous Carcinoma by Elucidating Its Early Change*”). The Development award has helped us to successfully compete for the Consortium award. Therefore, as communicated with the DoD OCRR officials, we have used the carryover fund to support the annual ovarian cancer symposium. Therefore, we will briefly summarize the progress report that is relevant during the last year and more specifically how we used the carryover budget to develop and/or support the ovarian cancer symposium.

The purpose of the Consortium are to **1)** elucidate the pathogenesis of ovarian cancer by characterizing the early lesions involved in the development of high-grade ovarian serous carcinoma, and **2)** to provide biomarkers for early ovarian cancer detection. Both goals will be facilitated by this Consortium Development plan which is a collaborative, interdisciplinary program that will establish the infrastructure to coordinate basic and translational research. Thus, the main purpose of the proposed Consortium Development project is to establish the infrastructure for supporting the subsequent Consortium research program focusing on identification and characterization of early molecular changes in ovarian cancer. The consortium is composed of four research sites and one Coordination center. The four research sites include Johns Hopkins University (JHU), Toronto University Health Network (TUHN), Memorial Sloan Kettering Cancer Center (MSKCC), and Yale University. The Coordination center will have three Cores (Administration, Biostatistics, and Pathology/Epidemiology) which will provide the essential support and integration of the projects from the research sites. JHU will be the Coordinating center with purview over the three Cores which in turn will coordinate the activities of the four research sites.

Dr. Kurman is the Director of the proposed Consortium development and will oversee the program. Dr. Kurman is currently the Director of Gynecologic Pathology at the Johns Hopkins Medical Institutions and has had a specific interest in gynecologic pathology for over 30 years. Dr. Kurman is a national and internationally recognized authority in the field of ovarian pathology and has published extensively on all types of ovarian neoplasms. Under the leadership of Dr. Kurman, the individual projects will act in a synergistic and highly integrated fashion aimed at better understanding the molecular landscape of early/precursor lesions of ovarian cancer in the subsequent consortium program project.

The scope of the Development award is briefly summarized. The Administrative Core will collect IRB protocols from all research sites, organize the Consortium symposium including the Pathology/ Epidemiology consensus meeting, setup and test the audio-video broad band electronic device for e-conference, organize the Internal Advisory Board, assemble research protocols for shared techniques. The Pathology/Epidemiology Core will define criteria for early ovarian cancer lesions (precursors) and select cases and controls, survey available cases and controls from all research sites, create one overall database for specimens with clinical and epidemiologic data, establish tissue processing and trafficking mechanisms, setup quality control procedures for DNA, RNA and protein extraction. The Biostatistics Core will establish the data collection, storage and security

system, perform power calculation, sample size justification and participate in study design for each project. Each research site will establish regular research conferences, formulate research specific aims, identify expert collaborators and consultants, and collaborate with Pathology/Epidemiology Core to identify pre-existing early lesions and precursors. The completion of these tasks is considered critical for us to continue our research in the Consortium research program and, in fact, this is the case. Of note, all the tasks have been done and as a result, we have been funded by the DoD consortium study.

Body

We have brought expertise of pathology, epidemiology, molecular techniques and tissue banking to focus on studying the pathogenesis of ovarian cancer development. The main tasks (according to the Statement of Work as originally submitted) that have been accomplished in this Development phase are followings. **First**, we have successfully brought together several institutions including Johns Hopkins University (JHU), Toronto University Health Network (TUHN), Memorial Sloan Kettering Cancer Center (MSKCC), and Yale University with clinics of women at high risk of developing ovarian cancer. We have set up a collaboration network of investigators at these institutions who have had a long-term interest in ovarian tumorigenesis, particularly in the characterization of molecular events related to the development of early lesions and their early detection. **Second**, we are creating a Coordination center to facilitate the interaction, integration and cohesion of this program. This goal has been achieved by establishing three Consortium Cores (Administration, Biostatistics, and Pathology/ Epidemiology). **Third**, we have set up different levels of communication to facilitate the interactions among investigators. **Finally**, we are inviting clinicians and patients to be active participants in this Consortium and they will work with the scientists to provide clinical insights into research projects. The details of progress are summarized in Table 1. We are fortunate that our consortium has been selected as the Consortium award in 2011. We have requested the “no-cost-extension” which has been granted by US AMRMC for another year to continue the tasks related to consortium development such as support for the incoming Ovarian Cancer Symposium and purchase of containers for slides and tissue blocks, etc. We have accomplished all the tasks and as a result, we move beyond the Development phase and are fully engaged in the consortium projects in W81XWH-11-2-0230.

Table 1. Tasks proposed in the Development phase and the status of accomplishment.

Tasks proposed	Accomplished
Administration Core (JHU)	<ul style="list-style-type: none">Organize the Consortium symposium including the Pathology/Epidemiology consensus meeting;Setup and test the audio-video broad band electronic device for e-conferences;Organize the Internal Advisory Board;

Pathology and Epidemiology Core (JHU)	<ul style="list-style-type: none"> Define criteria for early ovarian cancer lesions (precursors) and select cases and controls through the consensus meeting; Survey available cases and controls from all research sites; Establish tissue processing and trafficking mechanisms; Set up quality control procedures for DNA, RNA and protein extraction
Biostatistics Core (JHU)	<ul style="list-style-type: none"> Establish the data collection, storage and security systems; Perform power calculation and sample size justification for each project; Participate in study design of individual projects
Research sites (JHU, TUHN, MSKCC, Yale)	<ul style="list-style-type: none"> Establish regular research conferences at each site; Formulate research specific aims; Identify expert collaborators and consultants; Collaborate with Pathology/Epidemiology Core to identify pre-existing early lesions and precursors; Investigators have attended the DoD pre-award meeting at Fredrick

Key Research Accomplishments

We use the carryover budget to support in part of the 4th annual ovarian cancer symposium which was held at one of the research sites in this consortium- Memorial Sloan-Kettering Cancer Center on May 13-14, 2013. There are a total of more than 100 attendees including all the key persons from the DoD consortium program. Please see the following link for the detailed program: <https://www.mskcc.org/events/cme/prevention-and-early-detection-ovarian/form>

In addition, the symposium brought together the consortium key investigators and research advisory committee members to go over progress and potential problems. There were two internal meetings held during the symposium.

1st Meeting @ noon on May 13

Attendees: Dr Kurman, Dr Visvanathan, Dr Shih, Dr Wang, Dr Soslow, Dr Levine, Dr Parkash, Dr Shaw, Dr Twiggs, Dr Sophia George

Dr Visvanathan presented a proposal for a pilot study regarding tissue sampling to reduce cost of slide cuttings.

- Pilot study to assess prevalence/location of STICs
- Tissue selection in existing samples and prospective studies
- The need to have pathology reports to be uploaded before cases selection
- Selection of control cases STIC vs non-STIC

A review of published studies: Vicus 2010, Crumb/Falkins, Mehra

No data on exposure, as far as prevalence Mehra (Modern Pathology 2011) the top, middle and bottom of the blocks have been samples and 38% showed 1 STIC per block

Below are the questions for this pilot study

- 1- Clinical prevalence
- 2- How to improve clinical sampling and incorporate clinical reporting
- 3- Look for molecular and epidemiological associations identified in large studies
- 4- To spot prevention trends
- 5- Look for additional markers

Proposed study size is 94 cases which will be 24 cases per site. The sampling size is important to for the 5%< and >12% rule

Dr Soslow and Dr Parkash suggested to flip the block to prevent block exhaustion and for budget constraints

2nd Meeting @ 3:30pm on May 13

Attendees: Dr Kurman, Dr Visvanathan, Dr Shih, Dr Wang, Dr Soslow, Dr Levine, Dr Parkash, Dr Shaw, Dr Twiggs, Dr Sophia George, Dr Ellen Schildkraut, Dr Karen Wylie and 2 other grant officers via conference call

After Dr Kurman's brief introduction all PIs reviewed their projects. There were input and questions from PIs and attendees.

Reportable Outcomes

- The Consortium Development award has built up the necessary infrastructure to mature into a full Consortium program project which focuses on characterizing the early ovarian cancer lesions and precursors.
- This consortium has been selected for the second phase Ovarian Cancer Consortium award.
- As stated in the application, we have established the website for researchers and patients:
<http://www.ovariancancerprevention.org/>
- Publication from the Development award:
The Development award is used to support the ovarian cancer symposium. Therefore, there are no publications from this award.

Conclusion

We have used the carryover budget from the Consortium Development award to support in part the Ovarian Cancer Symposium held at the Memorial Sloan Kettering Cancer Center, New York in May 2013. The fund was used to cover the travel cost of principal investigators, research advisors and other key personnel. The symposium was considered successful as it brought together all investigators participated in DoD to present the

progress related to their projects and discuss the potential problems and future directions. In addition, this symposium serves as a platform for ovarian cancer researchers and patient advocates who are not the participants of the DoD consortium to appreciate the recent research advances from DoD consortium projects.

References

None.

Appendices

None.